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10/550,181	09/21/2005	Shailesh Bhamare	11336.1004USWO	1149

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EXAMINER	
SASAN, ARADHANA	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
12/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,181	BHAMARE ET AL.	
	Examiner	Art Unit	
	ARADHANA SASAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *19-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The remarks and amendments filed on 08/22/08 are acknowledged.

2. Claim 15 was amended. Claims 19-22 were withdrawn from consideration.

3. Claims 1-18 are included in the prosecution.

Response to Arguments

Claim Objections

4. In light of Applicant's amendment of claim 15, the claim objection of 05/22/08 is withdrawn.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-6 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Garg et al. (WO 03/063825) in view of Fülbreth et al. (US 5,151,433).

The claimed invention is a stabilized pharmaceutical solid composition comprising an ACE inhibitor and meglumine.

Garg teaches meglumine as an alkalinizing agent (Page 11, lines 1-3) and a therapeutically active moiety including the ACE inhibitor captropil (Page 10, lines 17-18) in a solid tablet formulation (Abstract).

Garg does not expressly teach ramipril as the ACE inhibitor.

Fülbreth teaches ACE inhibitors that are administered orally and solid formulations such as tablets or capsules (Col. 1, lines 40-42 and lines 53-56). Fülbreth teaches ramipril tablets stabilized against mechanical stress (Col. 4, lines 1-15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a solid tablet composition with meglumine and an ACE inhibitor, as suggested by Garg, use ramipril as the ACE inhibitor in the tablet formulation, as taught by Fülbreth, and produce the instant invention.

One of ordinary skill in the art would to do this because both Garg and Fülbreth teach solid tablet formulations with ACE inhibitors and it would be obvious to try an alternative ACE inhibitor, such as the ramipril taught by Fülbreth in the tablet of Garg during the process of routine experimentation. Furthermore, Fülbreth teaches ramipril tablets stabilized against mechanical stress (Col. 4, lines 1-15).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 1, the limitation of a stabilized solid composition would have been obvious over the stable tablet formulations taught by Garg. “The formulations can be expected to have a reasonable shelf life as shown by the accelerated stability data for 3 months, which demonstrates that the release profile is similar to that of initial

samples" (Page 23, lines 12-14). The limitation of an ACE inhibitor would have been obvious over the ACE inhibitor captropil taught by Garg (Page 10, lines 17-18). The limitation of meglumine would have been obvious over the meglumine taught by Garg (Page 11, lines 1-3).

Regarding instant claims 2-3, the limitation of ramipril would have been obvious over the ramipril taught by Fülbreth (Col. 4, lines 1-15).

Regarding instant claim 4, the limitation of 1mg to about 10mg ramipril in the composition would have been obvious over the 2.5mg ramipril tablets taught by Fülbreth (Col. 6, Table 1).

Regarding instant claims 5-6, the limitation of the ratio of ACE inhibitor to meglumine would have been obvious over the ratio of the therapeutically active ingredient (such as captopril) to the alkalinizing agent (meglumine) that is in the range of 0.1:9.9 to 7:3 (Page 11, lines 7-8) in view of the ramipril tablets taught by Fülbreth (Col. 6, Table 1). One with ordinary skill in the art would modify the ratio of the ACE inhibitor to the meglumine during the process of routine experimentation in order to achieve the desired dosage and stability criteria because this is a manipulatable parameter.

7. Claims 7-18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Garg et al. (WO 03/063825) in view of Fülbreth et al. (US 5,151,433) and further in view of Avrutov et al. (US 2002/0022646).

The teachings of Garg and Fülbreth with respect to the ACE inhibitor and meglumine are stated above.

Garg and Fülbreth do not expressly teach low substituted hydroxypropyl cellulose and pregelatinized starch.

Avrutov teaches tablet excipients including pregelatinized starch, low substituted hydroxypropyl cellulose and tableting lubricants like magnesium and calcium stearate (Page 4, [0038]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a solid tablet composition with meglumine and an ACE inhibitor, as suggested by Garg, use ramipril as the ACE inhibitor in the tablet formulation, as taught by Fülbreth, further use the low substituted hydroxypropyl cellulose and pregelatinized starch in the tablet formulation, as taught by Avrutov, and produce the instant invention.

One of ordinary skill in the art would to do this because the diluents low substituted hydroxypropyl cellulose and pregelatinized starch are known to be used in tablets, as evidenced by Avrutov. It would be obvious to use the commonly used diluents in the tablet formulations taught by Garg and Fülbreth.

Regarding instant claims 7-8, the diluents low substituted hydroxypropyl cellulose and pregelatinized starch would have been obvious over the pregelatinized starch and low substituted hydroxypropyl cellulose used as tableting excipients by Avrutov (Page 4, [0038]).

Regarding instant claim 9, the limitation of the ratio of ACE inhibitor to diluent would have been obvious over the pregelatinized starch and low substituted hydroxypropyl cellulose used as tableting excipients by Avrutov (Page 4, [0038]). One with ordinary skill in the art would find it obvious to modify the ratio of ACE inhibitor to diluent during the process of routine experimentation in order to optimize the tablet dosage and stability. The recited ratio would have been an obvious variant unless there is evidence of criticality or unexpected results.

Regarding instant claims 10-12, the limitation of the composition further comprising a lubricant would have been obvious over the magnesium stearate taught by Garg (Page 29, line 1) and by the magnesium and calcium stearate taught by Avrutov (Page 4, [0038]).

Regarding instant claims 13-14, the limitation of the amount of lubricant in the composition would have been obvious over the lubricant in the tablets taught by Garg (Page 29, line 1) and Avrutov (Page 4, [0038]) because one with ordinary skill in the art would modify the level of the lubricant in the formulation during the process of routine experimentation and the recited range would have been an obvious variant unless there is evidence of criticality or unexpected results.

Regarding instant claim 15, the stabilized pharmaceutical ACE inhibitor composition would have been obvious over the tablet with an ACE inhibitor and meglumine as taught by Garg (Page 11, lines 1-3, Page 10, lines 17-18 and Abstract) in view of the ramipril tablets stabilized against mechanical stress as taught by Fülbreth

(Col. 4, lines 1-15). The limitation of meglumine would have been obvious over the meglumine taught by Garg (Page 11, lines 1-3). The limitation of low substituted hydroxypropyl cellulose and pregelatinized starch would have been obvious over the pregelatinized starch and low substituted hydroxypropyl cellulose used as tableting excipients by Avrutov (Page 4, [0038]). The limitation of magnesium stearate would have been obvious over the magnesium stearate taught by Garg (Page 29, line 1) and by the magnesium stearate taught by Avrutov (Page 4, [0038]).

Regarding instant claims 16-18, the dosage form, capsule and tablet would have been obvious over the granules that are used to manufacture capsules or tablets (Col. 6, lines 21-23).

Response to Arguments

Rejection of claims 1-6 under 35 USC § 103(a)

8. Applicant's arguments, see Page 5, filed 08/22/08, with respect to the rejection of claims 1-6 under 35 USC § 103(a) as being unpatentable over Garg et al. (WO 03/063825) in view of Fülbreth et al. (US 5,151,433) have been fully considered but are not found persuasive.

Applicant argues that although the reference (Garg) discloses the possible use of captopril in a list of potential therapeutically active ingredients and meglumine in a list of potential alkalinizing agents, nothing in the reference points out any particular significance in using captopril, let alone using any ACE inhibitor along with meglumine. Applicant argues that captopril is merely mentioned with a large number of other therapeutically active ingredients having various chemical properties with completely

different stabilities in the presence of different excipients. Applicant argues that meglumine is mentioned along with a long list of other compounds, all of which are used to elevate the micro environmental pH of the core above the pKa of the active ingredient and thereby improve its solubility, as opposed to stabilizing an ACE inhibitor within a stabilized pharmaceutical solid composition.

This is not found persuasive because it would have been obvious to one of ordinary skill in the art at the time the invention was made to choose from a finite number of predictable active ingredients, including ACE inhibitors, and combine them with an alkalinizing agent such as meglumine, as disclosed by Garg, with a reasonable expectation of success of producing a functional product containing an ACE inhibitor and meglumine.

Applicant argues that meglumine also is entirely different from the other listed compounds with respect to its behavior in the presence of an ACE inhibitor, and as such, the reference provides no reason to select meglumine from the various pH elevating compounds and combine it with a drug that undergoes degradation at accelerated rates in the presence of commonly used pharmaceutical excipients such as ACE inhibitors as required by claim 1, nor any reason to expect that meglumine could be combined with an ACE inhibitor and achieve the benefit of superior stability shown in the present specification.

Applicant argues that Fülbreth does not remedy the deficiencies of Garg. Applicant argues that nothing in Fülbreth suggests combining an ACE inhibitor with meglumine, much less any reason to expect enhanced stability of the ACE inhibitor

within a pharmaceutical solid composition under various storage conditions, as demonstrated for example in the experimental work of the specification, could be achieved.

This is not found persuasive because the secondary reference, Fülbreth, teaches a method for stabilization of an active (including ramipril) as comprising: "coating the active substance or a mixture containing the active substance, with a polymeric protective film, or comprises mixing the active substance … with a physiologically tolerated buffer which ensures that a pH in the weakly acid to weakly alkaline range is set up in a formulation in the presence of moisture …" (emphasis added) (Col. 4, lines 1-15). Therefore, one of ordinary skill in the art would have the option of either coating the active substance with a polymeric protective film or mixing the active substance with a buffer. One of ordinary skill in the art would know that meglumine is a physiologically acceptable alkalinizing agent or buffer. Moreover, the primary reference, Garg, discloses meglumine as an alkalinizing agent that can be used in a composition with active substances such as ACE inhibitors (Page 11, lines 1-3).

Since all the claimed elements are found in Garg and Fülbreth, one with ordinary skill in the art could have combined the elements and the combination would have yielded predictable results. See *KSR International Co. v. Teleflex Inc.*, 550 U.S. - , 82 USPQ2d 1385 (2007).

Therefore, the rejection of 05/22/08 is maintained.

Rejection of claims 7-18 under 35 USC § 103(a)

9. Applicant's arguments, see Page 7, filed 08/22/08, with respect to the rejection of claims 7-18 under 35 USC § 103(a) as being unpatentable over Garg et al. (WO 03/063825) in view of Fülbreth et al. (US 5,151,433) and further in view of Avrutov et al. (US 2002/0022646) have been fully considered but are not found persuasive.

Applicant argues that Avrutov does not cure the deficiencies of Garg and Fülbreth. Applicants again respectfully contend that the rejection improperly uses hindsight in assessing the relevance of the reference. Applicant argues that the reference is directed to an economic process for preparing leflunomide in high yield and high purity, however, leflunomide is not relevant to the specific active ingredients indicated by Garg and Fülbreth. Applicant argues that Avrutov lists low substituted hydroxypropyl cellulose and pregelatinized starch among many other excipients that could be used.

This is not found persuasive because the deficiency of Garg and Fülbreth (low substituted hydroxypropyl cellulose and tableting lubricants like magnesium and calcium stearate) is remedied by Avrutov. Tableting diluents such as low substituted hydroxypropyl cellulose and pregelatinized starch are known in the art, as evidenced by Avrutov. One of ordinary skill in the art would try the tablet excipients from the finite list provided by Avrutov during the process of routine experimentation with a reasonable expectation of success in producing a functional tablet of ACE inhibitors, meglumine and tablet excipients.

Therefore, the rejection of 05/22/08 is maintained.

Conclusion

10. No claims are allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/ /MP WOODWARD/
Examiner, Art Unit 1615 Supervisory Patent Examiner, Art Unit 1615